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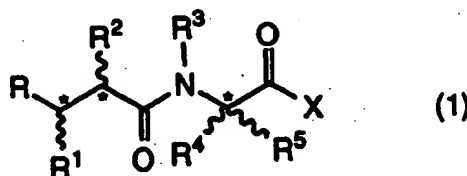


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(54) Title: PEPTIDYL DERIVATIVES AS METALLOPROTEINASE INHIBITORS		
(57) Abstract Compounds of formula (1) are described where R represents a -CONHOR ⁶ (where R ⁶ is a hydrogen atom or an acyl group), carboxyl (-CO ₂ H), esterified carboxyl, -SR ⁶ or -P(O)(X ¹ R ⁷)-X ² R ⁸ group, where X ¹ and X ² , which may be the same or different, is each an oxygen or sulphur atom and R ⁷ and R ⁸ , which may be the same or different each represents a hydrogen atom or an optionally substituted alkyl, aryl, or aralkyl group; R ¹ represents a hydrogen atom or an optionally substituted alkyl, alkenyl, aryl, aralkyl, heteroaralkyl or heteroarylthioalkyl group, R ² represents a group -Z ² (CH ₂) _m Z ¹ -Ar wherein Ar is an aryl or heteroaryl group, Z ¹ and Z ² , which may be the same or different, is each a bond or a heteroatom, and m is zero or an integer 1 to 6 with the proviso that when m is zero, Z ² is a bond, and Z ¹ is a heteroatom; R ³ represents a hydrogen atom or an alkyl group; R ⁴ represents a hydrogen atom or an alkyl group; R ⁵ represents a group -C(R ⁹)(R ¹⁰)Het-R ¹¹ , wherein R ⁹ and R ¹⁰ which may be the same or different is each an optionally substituted alkyl or alkenyl group optionally interrupted by one or more -O- or -S- atoms or -N(R ¹²)- groups (where R ¹² is a hydrogen atom or an optionally substituted alkyl group), or an optionally substituted cycloalkyl, cycloalkenyl, aryl or heteroaryl group, or R ⁹ and R ¹⁰ together with the carbon atom to which they are attached are linked together to form an optionally substituted cycloalkyl or cycloalkenyl group, Het is -O-, -S(O) _p - [where p is zero, or an integer 1 or 2] or -N(R ¹²)-, and R ¹¹ is a hydrogen atom or an aliphatic, cycloaliphatic, heterocycloaliphatic, aromatic, or heteroaromatic group; X is an amino (-NH ₂), substituted amino, hydroxyl or substituted hydroxyl group, or is linked to the atom of group Het in R ⁵ to form a chain -X-Alk-R ⁵ , where X is -N(R ¹²)-, Alk is an optionally substituted alkylene chain and R ⁵ is -Het-C(R ⁹)(R ¹⁰)-; and the salts, solvates, hydrates and prodrugs thereof. The compounds are orally active metalloproteinase inhibitors and in particular have a selective gelatinase action, have a long duration of action, and may be of use in the prophylaxis or treatment of diseases or disorders in which stromelysin, collagenase or gelatinase have a role, for example in the treatment of cancer to control the development of tumor metastases.		



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PEPTIDYL DERIVATIVES AS METALLOPROTEINASE INHIBITORS

5 FIELD OF THE INVENTION

This invention relates to a novel class of peptidyl derivatives, to processes for their preparation and to their use in medicine.

BACKGROUND TO THE INVENTION

- 10 In normal tissues, cellular connective tissue synthesis is offset by extracellular matrix degradation, the two opposing effects existing in dynamic equilibrium. Degradation of the matrix is brought about by the action of proteinases released from resident connective tissue cells and invading inflammatory cells, and is due, in part, to the activity of at least
- 15 three groups of metalloproteinases. These are the collagenases, the gelatinases (or type-IV collagenases) and the stromelysins. Normally these catabolic enzymes are tightly regulated at the level of their synthesis and secretion and also at the level of their extracellular activity, the latter through the action of specific inhibitors, such as α_2 -
- 20 macroglobulins and TIMP (tissue inhibitor of metalloproteinase), which form inactive complexes with metalloproteinases.

- The accelerated, uncontrolled breakdown of connective tissues by metalloproteinase catalysed resorption of the extracellular matrix is a
- 25 feature of many pathological conditions, such as rheumatoid arthritis, corneal, epidermal or gastric ulceration; tumour metastasis or invasion; periodontal disease and bone disease. It can be expected that the pathogenesis of such diseases is likely to be modified in a beneficial manner by the administration of metalloproteinase inhibitors and
- 30 numerous compounds have been suggested for this purpose [for a general review see Wahl, R.C. *et al* Ann. Rep. Med. Chem. 25, 175-184, Academic Press Inc., San Diego (1990)].

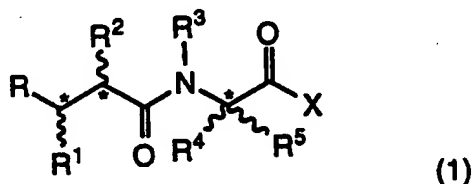
- Although numerous metalloproteinase inhibitors have been described,
- 35 many have not been suitable for further development as medicines since they have lacked any useful activity when administered orally at

pharmaceutically acceptable doses. What is therefor needed is a potent and selective orally active compound with a good duration of action.

5 SUMMARY OF THE INVENTION

We have now found a new class of peptidyl derivatives, members of which are metalloproteinase inhibitors and which, in particular, advantageously possess a potent and selective inhibitory action against gelatinase. In addition, compounds according to the invention have
10 surprisingly good oral bioavailability, and after oral administration have an advantageously longer duration of action than related known compounds, such as those described in International Patent Specification No. WO92/09564.

15 Thus according to one aspect of the invention we provide a compound of formula (1)



wherein R represents a -CONHOR⁶ [where R⁶ is a hydrogen atom or an acyl group], carboxyl (-CO₂H), esterified carboxyl, -SR⁶ or -P(O)(X¹R⁷)-
20 -X²R⁸ group, where X¹ and X², which may be the same or different, is each an oxygen or sulphur atom and R⁷ and R⁸, which may be the same or different each represents a hydrogen atom or an optionally substituted alkyl, aryl, or aralkyl group;

25 R¹ represents a hydrogen atom or an optionally substituted alkyl, alkenyl, aryl, aralkyl, heteroaralkyl or heteroarylthioalkyl group;

R² represents a group -Z²(CH₂)_mZ¹-Ar wherein Ar is an aryl or heteroaryl group, Z¹ and Z², which may be the same or different, is each
30 a bond or a heteroatom, and m is zero or an integer 1 to 6 with the proviso that when m is zero, Z² is a bond, and Z¹ is a heteroatom;

R³ represents a hydrogen atom or an alkyl group;

R⁴ represents a hydrogen atom or an alkyl group;

5 R⁵ represents a group -C(R⁹)(R¹⁰)Het-R¹¹, wherein R⁹ and R¹⁰ which may be the same or different is each an optionally substituted alkyl or alkenyl group optionally interrupted by one or more -O- or -S- atoms or -N(R¹²)- groups (where R¹² is a hydrogen atom or an optionally substituted alkyl group), or an optionally substituted cycloalkyl, cycloalkenyl, aryl or heteroaryl group, or R⁹ and R¹⁰ together with the carbon atom to which they are attached are linked together to form an optionally substituted cycloalkyl or cycloalkenyl group, Het is -O-, -S(O)_p- [where p is zero, or an integer 1 or 2] or -N(R¹²)-, and R¹¹ is a hydrogen atom or an aliphatic, cycloaliphatic, heterocyclo-aliphatic, aromatic, or hetero-
10 aromatic group;

X is an amino (-NH₂), substituted amino, hydroxyl or substituted hydroxyl group, or is linked to the atom or group Het in R⁵ to form a chain -X-Alk-R⁵- where X is -N(R¹²)-, Alk is an optionally substituted alkylene chain and R⁵ is -Het-C(R⁹)(R¹⁰)-;
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and the salts, solvates, hydrates and prodrugs thereof.

It will be appreciated that the compounds according to the invention can
25 contain one or more asymmetrically substituted carbon atoms, for example those marked with an asterisk in formula (1). The presence of one or more of these asymmetric centres in a compound of formula (1) can give rise to stereoisomers, and in each case the invention is to be understood to extend to all such stereoisomers, including enantiomers
30 and diastereoisomers, and mixtures, including racemic mixtures, thereof.

In the formulae herein, the ~line is used at a potential asymmetric centre to represent the possibility of R- and S- configurations, the — line and the ----- line to represent an unique configuration at an asymmetric
35 centre.

In the compounds according to the invention, when the group R represents an esterified carboxyl group, it may be for example a group of formula $-\text{CO}_2\text{R}^{13}$ where R^{13} is a straight or branched, optionally substituted C_{1-8} alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a C_{6-12} aryl C_{1-8} alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, α -naphthylmethyl or β -naphthylmethyl group; a C_{6-12} aryl group such as an optionally substituted phenyl, α -naphthyl or β -naphthyl group; a C_{6-12} aryloxy C_{1-8} alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, α - or β -naphthyloxymethyl group; an optionally substituted C_{1-8} alkanoyloxy C_{1-8} alkyl group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a C_{6-12} aroxyloxy C_{1-8} alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group. Optional substituents present on the groups R^{13} include for example one or more halogen atoms such as fluorine, chlorine, bromine or iodine atoms, or C_{1-4} alkyl, e.g. methyl or ethyl, or C_{1-4} alkoxy, e.g. methoxy or ethoxy, groups.

In general, when the group R represents an esterified carboxyl group, it may be a metabolically labile ester of a carboxylic acid.

When the group R^6 in compounds of formula (1) represents an acyl group, it may be for example a group of formula $\text{R}^{14}\text{C}=\text{X}^3$ where X^3 is an oxygen or sulphur atom and R^{14} represents a hydrogen atom or a group selected from amino ($-\text{NH}_2$), substituted amino (for example a group $-\text{NR}^{17}\text{R}^{18}$ as described below in relation to the group X), or an optionally substituted C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkythio, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-12} aryl, C_{6-12} aralkyl, C_{3-6} cycloalkyl, C_{3-6} heteroaryl or C_{3-6} heteroaralkyl group. Particular groups of these types include optionally substituted methyl, ethyl, n-propyl, i-propyl, methoxy, ethoxy, methylthio, ethylthio, ethenyl, 1-propenyl, ethynyl, 1-propynyl, phenyl, 1-naphthyl, 2-naphthyl, benzyl, phenethyl, 1-naphthylmethyl, 2-naphthylmethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, furanyl, pyrrolyl, thienyl, furanylmethyl, pyrrolylmethyl or thienylmethyl groups. Optional substituents which may be present on such R^{14} groups include one or more substituents selected from those described below in relation to the

group R¹ or R² when such groups represent substituted alkyl, aryl or heteroaryl groups.

5 The group R⁷ and/or R⁸ in compounds of formula (1) may each be a hydrogen atom or an optionally substituted straight or branched C₁₋₆ alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or i-butyl, C₆₋₁₂aryl, e.g. phenyl, or C₆₋₁₂arylC₁₋₆alkyl, e.g. benzyl, phenylethyl or phenylpropyl group. Optional substituents present on alkyl groups of this type include one or more C₁₋₆alkoxy, e.g. methoxy or ethoxy, or C₁₋₆alkylthio, 10 e.g. methylthio or ethylthio groups or an optionally substituted C₆₋₁₂ aryloxy e.g. phenyloxy, C₆₋₁₂arylthio e.g. phenylthio, C₆₋₁₂arylC₁₋₆alkoxy e.g. benzyloxy or C₆₋₁₂arylC₁₋₆alkylthio e.g. benzylthio. Optional substituents present on the group R⁷ or R⁸ when it is an aryl or aralkyl group or an alkyl group substituted by an aryloxy or arylthio group 15 include R¹⁶ groups as defined below.

When the group R¹ in compounds of formula (1) represents an optionally substituted alkyl or alkenyl group, it may be, for example, a straight or branched C₁₋₆alkyl or C₂₋₆alkenyl group, such as a methyl, ethyl, 20 n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, n-hexyl, ethenyl, 1-propenyl, 1-butenyl or 2-butenyl group optionally substituted by one or more C₁₋₆alkoxy, e.g. methoxy, ethoxy, propoxy, C₁₋₆alkylthio, e.g. methylthio, ethylthio, propylthio, C₆₋₁₂arylC₁₋₆alkoxy, e.g. phenylC₁₋₆alkoxy such as benzyloxy, aralkylthio, e.g. phenyl 25 C₁₋₆alkylthio such as benzylthio, amino (-NH₂), substituted amino, [such as -NHR¹⁵, where R¹⁵ is a C₁₋₆ alkyl e.g. methyl or ethyl, C₆₋₁₂ arylC₁₋₆alkyl, e.g. phenylC₁₋₆alkyl, such as benzyl, C₆₋₁₂aryl, e.g. phenyl, C₃₋₈cycloalkyl, e.g. cyclohexyl, or C₃₋₈cycloalkylC₁₋₆alkyl, e.g. cyclohexyl methyl group], carboxyl (-CO₂H) or -CO₂R¹³ [where R¹³ is as 30 defined above] groups.

Aryl groups represented by R¹ in compounds of formula (1) include optionally substituted mono- or bicyclic C₆₋₁₂ aryl groups such as phenyl or 1- or 2-naphthyl groups.

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Aralkyl groups represented by R¹ include optionally substituted mono- or

bicyclic C₆₋₁₂arylC₁₋₆alkyl groups such as phenylC₁₋₆alkyl, or 1- or 2-naphthylC₁₋₆alkyl, for example benzyl, phenylethyl, phenylpropyl, phenylbutyl, phenylpentyl, 1- or 2-naphthylmethyl, naphthylethyl, naphthylpropyl, naphthylbutyl or naphthylpentyl groups.

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When the group R¹ in compounds of formula (1) is a heteroaralkyl group, it may be for example an optionally substituted mono- or bicyclic C₃₋₉heteroarylC₁₋₆alkyl group, such as an optionally substituted pyrrolylmethyl, furanylmethyl, thienylmethyl, imidazolylmethyl, oxazolylmethyl, thiazolylmethyl, pyrazolylmethyl, pyridinylmethyl, or pyrimidinylmethyl group.

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Heteroarylthioalkyl groups represented by R¹ include optionally substituted mono- or bicyclic C₃₋₉heteroarylthioC₁₋₆alkyl groups such as optionally substituted pyrrolylthiomethyl, furanylthiomethyl, oxazolylthiomethyl, thiazolylthiomethyl, pyrazolylthiomethyl, pyridinylthiomethyl, or pyrimidinylthiomethyl groups.

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Optional substituents which may be present on aryl, aralkyl, heteroaralkyl or heteroarylthioalkyl groups represented by R¹ include those R¹⁶ substituents discussed below.

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When the group Ar in compounds of formula (1) is an aryl group it may be an optionally substituted mono- or bicyclic C₆₋₁₂aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group. When the group Ar is a heteroaryl group it may be an optionally substituted mono- or bicyclic C₃₋₉heteroaryl group containing one, two or three heteroatoms, selected from -O- or -S-, or -N(R¹²)- groups. Particular examples include optionally substituted pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, pyridinyl or pyrimidinyl groups. It will be appreciated that such groups may be connected to the remainder of the compound of formula (1) through any ring carbon atom, or where appropriate through a heteroatom or group -N(R¹²)-.

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The aryl, aralkyl, heteroaryl, heteroaralkyl or heteroarylthioalkyl groups represented by R¹ and/or Ar in compounds of formula (1) may each

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optionally be substituted in the cyclic part of the group by one, two or more substituents [R¹⁶] selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or C₁₋₆alkyl, e.g. methyl or ethyl, C₁₋₆alkoxy e.g. methoxy or ethoxy, C₂₋₆alkylenedioxy, e.g. ethylenedioxy, haloC₁₋₆alkyl, e.g. trifluoromethyl, C₁₋₆alkylamino, e.g. methylamino or ethylamino, C₁₋₆dialkylamino, e.g. dimethylamino or diethylamino, amino (-NH₂), nitro, cyano, hydroxyl (-OH), carboxyl (-CO₂H), -CO₂R¹³, where R¹³ is as defined above, C₁₋₆alkylcarbonyl, e.g. acetyl, sulphonyl (-SO₃H), C₁₋₆alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl (-SO₂NH₂), C₁₋₆alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C₁₋₆dialkylaminosulphonyl e.g. dimethylaminosulphonyl or diethylaminosulphonyl, carboxamido (-CONH₂), C₁₋₆alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylamino-carbonyl, C₁₋₆dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, sulphonylamino (-NH₂SO₂H), C₁₋₆alkylsulphonyl-amino, e.g. methylsulphonylamino or ethylsulphonylamino, or C₁₋₆dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonyl-amino groups. It will be appreciated that where two or more R¹⁶ substituents are present, these need not necessarily be the same atoms and/or groups. The R¹⁶ substituents may be present at any ring carbon atom away from that attached to the rest of the molecule of formula (1). Thus, for example, in phenyl groups any substituents may be present at the 2-, 3-, 4-, 5- or 6-positions relative to the ring carbon atom attached to the remainder of the molecule.

25

When the group -(CH₂)_m- in compounds of formula (1) is a group -(CH₂)₂₋₆ it will be appreciated that such groups may be either straight or branched.

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Heteroatoms represented by Z¹ and/or Z² in compounds of formula (1) include -O- or -S- atoms.

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When the groups R³ and R⁴ in compounds of formula (1) are alkyl groups, they may be for example straight or branched C₁₋₆alkyl groups such as methyl or ethyl groups.

When the group R^9 or R^{10} in compounds of formula (1) is an optionally substituted alkyl or alkenyl group it may be a straight or branched C_{1-6} alkyl, e.g. methyl, ethyl, n-propyl i-propyl, n-butyl, i-butyl, n-pentyl or n-hexyl or C_{2-6} alkenyl e.g. ethenyl or 1-propenyl group optionally interrupted by one or more -O- or -S- atoms or -N(R^{12})- groups where R^{12} is a hydrogen atom or an optionally substituted C_{1-6} alkyl group such as a methyl, ethyl or propyl group.

Optional substituents which may be present on such groups include one or more C_{1-6} alkoxy, C_{1-6} alkylthio, C_{6-12} aryl C_{1-6} alkoxy, aralkylthio, amino, substituted amino, carboxyl or $-CO_2R^{13}$ groups as defined above in connection with the group R^1 , or an optionally substituted cycloalkyl, cycloalkenyl, aryl or heteroaryl group as defined below in connection with the groups R^9 and R^{10} .

When the group R^9 , R^{10} or R^9 and R^{10} together with the carbon atom to which they are attached, is an optionally substituted cycloalkyl or cycloalkenyl group, it may be for example a C_{3-8} cycloalkyl, e.g. cyclopropyl, cyclopentyl or cyclohexyl, or C_{3-8} cycloalkenyl e.g. cyclopropenyl, cyclopentenyl or cyclohexenyl, group optionally substituted by one, two or more C_{1-6} alkyl, e.g. methyl or ethyl, C_{1-6} alkoxy, e.g. methoxy or ethoxy, C_{1-6} alkylthio, e.g. methylthio, or hydroxyl groups. Alternatively, the group R^9 or R^{10} may be an aryl or heteroaryl group as defined above for the group Ar.

The term Het in compounds of formula (1) may represent -O-, -S-, -S(O)-, -S(O)₂- or -N(R^{12})- where R^{12} is a hydrogen atom or a C_{1-6} alkyl group as defined above.

When R^{11} in compounds of formula (1) is an aliphatic group it may be for example an optionally substituted saturated or unsaturated straight or branched C_{1-6} alkyl chain optionally interrupted by one or more -O- or -S- atoms or groups selected from -N(R^{12})-, -CO-, -CON(R^{12})-, or -N(R^{12})CO-. Particular groups include optionally substituted methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, ethenyl, 1-propenyl, 1-butenyl or 2-butenyl groups. Optional substituents which may be present on groups of

these types include one or more amino ($-NH_2$), substituted amino [for example a group $-NR^{17}R^{18}$ as described below in relation to the group X], C_{6-12} aryl, .g. optionally substituted phenyl, C_{6-12} aryloxy e.g. optionally substituted phenoxy, [the optional substituents in each case being R^{16} groups as defined above], C_{3-8} cycloalkyl, e.g. cyclopentyl or cyclohexyl, C_{3-8} cycloalkoxy, e.g. cyclopentyloxy or cyclohexyloxy, carboxyl ($-CO_2H$) or $-CO_2R^{13}$ groups.

Cycloaliphatic groups represented by R^{11} in compounds of formula (1) include optionally substituted C_{3-8} cycloalkyl and C_{3-8} cycloalkenyl groups, for example optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentenyl and cyclohexenyl groups. Optional substituents include those groups R^{16} described above.

Heterocycloaliphatic groups represented by R^{11} in the compounds of formula (1) include optionally substituted C_{5-7} heterocycloalkyl groups containing one or two heteroatoms selected from -O- or -S-, or a group $-N(R^{12})-$, for example optionally substituted piperazinyl, morpholinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, or N-methylpiperidinyl groups. Optional substituents include those groups R^{16} described above. The heterocycloalkyl groups represented by R^{11} may be attached to the remainder of the molecule through any ring carbon atom.

When the group R^{11} in compounds of formula (1) is an aromatic group it may be for example an optionally substituted mono- or bicyclic C_{6-12} aryl group, for example an optionally substituted phenyl or 1- or 2-naphthyl group. Optional substituents which may be present on groups of this type include those R^{16} substituents described above.

Heteroaromatic groups represented by the group R^{11} include mono- or bicyclic C_{5-9} heteroaromatic groups containing one, two or three heteroatoms selected from -O- or -S-, or $-N(R^{12})$ groups. Particular examples include pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, 1-indolyl, 2-indolyl, 1-quinolinyl or 2-quinolinyl groups. Such groups may be optionally substituted, for example by one or more R^{16}

substituents. The heteroaromatic group may be connected to the remainder of the compound of formula (1) through any ring carbon atom, or where appropriate through a heteroatom or group -N(R¹²)-.

5 When X in the compounds of formula (1) represents a substituted amino group it may be for example a group of formula -NR¹⁷R¹⁸, where R¹⁷ and R¹⁸, which may be the same or different, is each a hydrogen atom (with the proviso that when one of R¹⁷ or R¹⁸ is a hydrogen atom, the other is not) or an optionally substituted straight or branched alkyl group, optionally interrupted by one or more -O- or -S- atoms or -N(R¹²)- or
10 aminocarbonyloxy [-NHC(O)O-] groups or R¹⁷ and R¹⁸, together with the nitrogen atom to which they are attached, may form an optionally substituted C₃₋₆cyclic amino group optionally possessing one or more other heteroatoms selected from -O- or -S-, or -N(R¹²)- groups.

15 When R¹⁷ and/or R¹⁸ is an alkyl group it may be for example a C₁₋₆alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, or t-butyl group, optionally interrupted by one or more -O- or -S- atoms, or -N(R¹³)- or aminocarbonyloxy groups and may be for example a
20 methoxymethyl, ethoxymethyl, ethoxymethyl, ethoxyethyl or ethyl-aminocarbonyloxymethyl group. The optional substituents which may be present on such groups include hydroxyl (-OH), carboxyl (-CO₂H), esterified carboxyl (-CO₂R¹³), carboxamido (-CONH₂), substituted carboxamido, e.g. a group -CONR¹⁷R¹⁸ where NR¹⁷R¹⁸ is as defined
25 herein, amino (-NH₂), substituted amino, for example a group of formula -NR¹⁷R¹⁸, aminosulphonylamino, for example -N(R¹²)SO₂NH₂ or -N(R¹²)SO₂NR¹⁷R¹⁸ or aryl, e.g. C₆₋₁₂ aryl such as phenyl, optionally substituted by one, two or more R¹⁶ substituents selected from those listed above.

30 Particular examples of cyclic amino groups represented by -NR¹⁷R¹⁸ include morpholinyl, imidazolyl, piperazinyl, pyrrolyl, oxazolyl, thiazolyl, pyrazolyl, pyrrolidinyl, pyridinyl and pyrimidinyl groups.

35 When the group X is a substituted hydroxyl group it may be for example a group -OR¹¹ where R¹¹ is as defined above, other than a hydrogen atom.

When X is linked to the atom or group Het in R⁵ to form a chain -X-Alk-R⁵-, the optionally substituted alkylene chain represented by Alk may be an optionally substituted straight or branched C₂₋₉ alkylene chain, for example an ethylene, propylene or butylene chain. Optional substituents present on the alkylene chain include those described above in relation to the alkyl group represented by R². In compounds of this type, the group X is -N(R¹²)-, where R¹² is as defined above. The group R⁵ is -Het-C(R⁹)(R¹⁰)- where Het, R⁹ and R¹⁰ are as defined above.

10

Salts of compounds of formula (1) include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, such as hydrochlorides, hydrobromides, hydroiodides, p-toluene sulphonates, phosphates, sulphates, perchlorates, acetates, trifluoroacetates, propionates, citrates, malonates, succinates, lactates, oxalates, tartarates and benzoates.

20

Salts may also be formed with bases. Such salts include salts derived from inorganic or organic bases, for example alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

25

Prodrugs of compounds of formula (1) include those compounds, for example esters, alcohols or amines, which are convertible, *in vivo*, by metabolic means, e.g. by hydrolysis, reduction, oxidation or transesterification.

30

When the group R in compounds of the invention is an esterified carboxyl group, it may be a metabolically labile ester of formula -CO₂R¹³ where R¹³ may be an ethyl, benzyl, phenylethyl, phenylpropyl, 1- or 2-naphthyl, 2,4-dimethylphenyl, 4-t-butylphenyl, 2,2,2-trifluoroethyl, 1-(benzyloxy)-benzyl, 1-(benzyloxy)ethyl, 2-methyl-1-propionyloxypropyl, 2,4,6-trimethylbenzoyloxymethyl or pivaloyloxymethyl group.

35

When the group R in compounds of formula (1) is a -P(O)(X¹R⁷)X²R⁸

group it may in particular be a $P(O)(OR^7)OR^8$, .g. a $-P(O)(OH)OR^8$ group, or a $-P(O)(SH)OR^8$ or $-P(O)(OH)SR^8$ group. Examples of such groups include $-P(O)(OCH_3)OCH_3$, $-P(O)(OCH_2CH_3)OCH_2CH_3$, $-P(O)(OH)OH$, $-P(O)(OH)SH$, $-P(O)(SH)OH$, $-P(O)(OH)OCH_3$,
 5 $-P(O)(OH)SCH_3$, $-P(O)(OH)OCH_2CH_3$, $-P(O)(OH)OPh$, $-P(O)(OH)SPh$, $-P(O)(OH)OCH_2Ph$ or $-P(O)(OH)SCH_2Ph$, where Ph is a phenyl group optionally substituted by one or more substituents R^{16} .

10 In the compounds of formula (1) the group R^1 may in particular be a C_{1-6} alkyl group such as a methyl group, an aralkyl group such as benzyl group, an arylthioalkyl group such as a phenylthiomethyl group or a heteroarylthioalkyl group such as thienylthiomethyl, pyridinylthiomethyl or pyrimidinylthiomethyl group or is especially a hydrogen atom.

15 The group R^2 in compounds of formula (1) may in particular be an $ArO-$, $ArS-$, $ArCH_2-$, $Ar(CH_2)_2-$, $Ar(CH_2)_3-$, $Ar(CH_2)_4-$, $ArOCH_2-$, $ArO(CH_2)_2-$, $ArO(CH_2)_3-$, $ArO(CH_2)_4-$, $ArSCH_2-$, $ArS(CH_2)_2-$, $ArS(CH_2)_3-$, or $ArS(CH_2)_4-$ group, where Ar is as defined for formula (1). Particular groups of these types are those wherein Ar is an optionally substituted
 20 phenyl, pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, pyridinyl or pyrimidinyl group. Optional substituents present on Ar groups of these types include one, two or more R^{16} substituents as defined above.

25 The groups R^3 and R^4 in compounds of formula (1) may each in particular be a methyl group, or, especially, a hydrogen atom.

The group R^5 in compounds of formula (1) may in particular be a group $-C(R^9)(R^{10})Het-R^{11}$ where R^9 and R^{10} are the same. Particular
 30 compounds of this type are those wherein R^9 and R^{10} is each the same and is each an optionally substituted alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl or heteroaryl group.

35 In another group of compounds of formula (1) the group R^5 may be a group $-C(R^9)(R^{10})Het-R^{11}$ where R^{11} is an aliphatic, cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group as described

above for compounds of formula (1).

5 The group X in compounds of formula (1) may be in particular an amino (-NH₂) or -NR¹⁷R¹⁸ group. Particular -NR¹⁷R¹⁸ groups are -NHR¹⁸ groups. Groups of this type include those where R¹⁸ is a C₁₋₆alkyl group, for example a methyl, ethyl, or n-propyl group, optionally interrupted by one or more -O- or -S- atoms or -N(R¹²) [e.g. -NH- or -N(CH₃)-] or aminocarbonyloxy groups and optionally substituted by a hydroxyl, carboxyl, carboxyalkyl, e.g. carboxymethyl, carboxamido, amino, 10 -NR¹⁷R¹⁸, [for example di-C₁₋₆alkylamino such as dimethylamino, C₁₋₆alkylamino such as methylamino, or C₃₋₆ cyclic amino such as morpholinyl, pyrrolidinyl or pyridinyl] or phenyl optionally substituted by one, two or more R¹⁶ substituents.

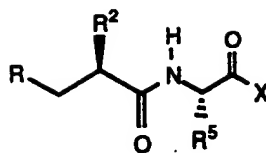
15 A particularly useful group of compounds according to the invention is that of formula (1) wherein R⁵ is a group -C(R⁹)(R¹⁰)Het-R¹¹ where Het is -S(O)_p and R⁹, R¹⁰ and R¹¹ are as defined for formula (1). Compounds of this type wherein Het is -S- are particularly useful.

20 A further particularly useful group of compounds of formula (1) are those wherein X is an amino or substituted amino group. Particularly useful compounds of this type are those wherein X is -NHCH₃ or, especially, -NH₂.

25 In general, in compounds of formula (1) the groups R¹, R³ and R⁴ is each preferably a hydrogen atom.

30 In a further preference, the group R in compounds according to the invention is a -CONHOH or a -CO₂H group or a metabolically labile ester thereof, or a group P(O)(OH)OR⁸. In a particular preference, however, R is a -CO₂H, -P(O)(OH)₂ or, especially, a -CONHOH group.

An especially useful group of compounds according to the invention has the formula (1a)



(1a)

wherein R, R², R⁵ and X are as defined for formula (1); and the salts, solvates, hydrates and prodrugs thereof.

- 5 A particularly useful group of compounds of formula (1a) are those wherein R represents a -CONHOH, -CO₂H or -P(O)(OH)₂ group; R² and R⁵ are as defined for formula (1); X is an amino (-NH₂) or substituted amino group; and the salts, solvates, hydrates and prodrugs thereof.
- 10 Particularly useful compounds of formula (1a) are those wherein R⁵ is a group -C(R⁹)(R¹⁰)S(O)_pR¹¹. Compounds of this type in which R⁵ is a -C(R⁹)(R¹⁰)SR¹¹ group are especially useful.
- 15 Other useful compounds of formula (1a) include those wherein R² represents an ArO-, ArS-, ArCH₂-, Ar(CH₂)₂-, Ar(CH₂)₃-, Ar(CH₂)₄-, ArOCH₂-, ArO(CH₂)₂-, ArO(CH₂)₃-, ArO(CH₂)₄-, ArSCH₂-, ArS(CH₂)₂-, ArS(CH₂)₃-, or ArS(CH₂)₄- group, where Ar is as defined for formula (1), and especially is an optionally substituted phenyl group. Particularly useful groups of this type are optionally substituted phenylethyl,
 - 20 phenylpropyl, or phenylbutyl groups. Optionally substituted phenylpropyl groups are especially useful. Optional substituents on the phenyl group may be one, two or more R groups as defined for compounds of formula (1). Particularly useful substituted phenyl groups are 4-substituted phenyl groups.
 - 25 In the compounds of formula (1a) X may be a -NH₂ group or a group -NR¹⁷R¹⁸ as defined for compounds of formula (1), particularly a -NHR¹⁸ group.
 - 30 An especially useful group of compounds according to the invention has the formula (1a) wherein R² is an optionally substituted phenylC₃₋₆alkyl group, especially an optionally substituted phenylpropyl or phenylbutyl group, R⁵ is a group -C(R⁹)(R¹⁰)SR¹¹ where R⁹ and R¹⁰ is each the

same and is each an optionally substituted C₁₋₆ alkyl group, and R¹¹ is as defined for formula (1); and X is an amino (-NH₂) or -NHR¹⁸ group, particularly where R¹⁸ is an optionally substituted C₁₋₆ alkyl group. Compounds of this type wherein R⁵ is a group -C(CH₃)₂SR¹¹ are particularly useful, especially where the group R¹¹ is a hydrogen atom or an optionally substituted saturated C₁₋₆ alkyl chain. In compounds of this last type X is preferably an amino (-NH₂) group or a -NHCH₃ group.

In a still further useful group of compounds of formula (1a), R is a -CONHOH, -CO₂H or -P(O)(OH)₂ group, R² is an optionally substituted phenylpropyl group, R⁵ is a group -C(CH₃)₂SR¹¹ where R¹¹ is a hydrogen atom or an optionally substituted C₁₋₆ alkyl group, and X is an amino (-NH₂) or -NHR¹⁸ group where R¹⁸ is an optionally substituted C₁₋₆ alkyl group. Compounds of this type wherein R is a -CONHOH group are particularly useful; as are those compounds wherein R¹¹ is a hydrogen atom or a methyl group; and those compounds wherein R¹⁸ is a hydrogen atom or a methyl group.

One further group of compounds according to the invention has the formula (1a) wherein R and R² are as defined for formula (1), R⁵ is a group -C(CH₃)₂SH or -C(CH₃)₂SCH₃ and X is -NH₂ or -NHCH₃. Particularly useful compounds of this type are those wherein R is a group -CONHOH, -CO₂H or -P(O)(OH)₂ and R² is a group ArO-, ArS-, ArCH₂-, Ar(CH₂)₂-, Ar(CH₂)₃-, Ar(CH₂)₄-, ArOCH₂-, ArO(CH₂)₃-, ArO(CH₂)₄-, ArSCH₂-, ArS(CH₂)₂-, ArS(CH₂)₃- or ArS(CH₂)₄- group, where Ar is as defined for formula (1). Especially useful compounds of this type are those wherein Ar is an optionally substituted phenyl group. Particularly useful compounds are those where R² is an optionally substituted phenylethyl, phenylbutyl or, especially, phenylpropyl group.

In compounds of the above described types, R² is preferably an optionally substituted phenylpropyl group and R⁵ is preferably a group -C(CH₃)₂SCH₃. In these compounds, R is preferably -CO₂H or -P(O)(OH)₂ or is especially -CONHOH. X is preferably -NH₂ or -NHCH₃.

Important compounds according to the invention include:

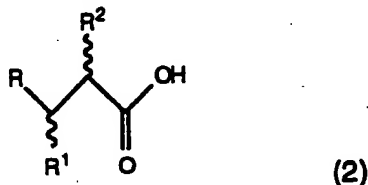
- [4-(N-Hydroxyamino)-2(R)-[3-(4-chlorophenyl)propyl]succinyl]-L-[S-(methyl)penicillamine] N-methylamide;
[4-(N-Hydroxyamino)-2(R)-[3-(4-chlorophenyl)propyl]succinyl]-L-[S-(methyl)penicillamine] amide;
5 [4-(N-Hydroxyamino)-2(R)-[3-(4-chlorophenyl)propyl]succinyl]-L-penicillamine amide;
[4-(N-Hydroxyamino)-2(R)-[3-(4-chlorophenyl)propyl]succinyl]-L-[S-(methyl)penicillaminesulphone]-N-methylamide;
10 [4-(N-Hydroxyamino)-2(R)-[3-(4-chlorophenyl)propyl]succinyl]-L-[S-(methyl)penicillaminesulphoxide]-N-methylamide;
[4-(N-Hydroxyamino)-2(R)-[3-(4-chlorophenyl)propyl]succinyl]-L-penicillamine-N-methylamide;
and the salts, solvates, hydrates and prodrugs thereof.

15

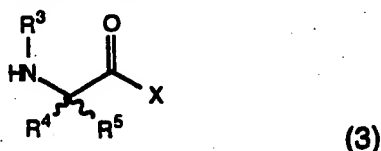
- The compounds according to the invention may be prepared by the following general processes, more specifically described in the Examples hereinafter. In the description and formulae below the groups R, R¹, R², R³, R⁴, R⁵ and X are as defined above, except where otherwise
20 indicated. It will be appreciated that functional groups, such as amino, hydroxyl or carboxyl groups, present in the various compounds described below, and which it is desired to retain, may need to be in protected form before any reaction is initiated. In such instances, removal of the protecting group may be the final step in a particular
25 reaction. Suitable amino or hydroxyl protecting groups include benzyl, benzyloxycarbonyl or t-butyloxycarbonyl groups. These may be removed from a protected derivative by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an alcohol e.g. methanol, or
30 by treatment with trimethylsilyl iodide or trifluoroacetic acid in an aqueous solvent. Suitable carboxyl protecting groups include benzyl groups, which may be removed from a protected derivative by the methods just discussed, or alkyl groups, such as a t-butyl group which may be removed from a protected derivative by treatment with trifluoroacetic acid
35 in an aqueous solvent. Other suitable protecting groups and methods for their use will be readily apparent. The formation of the protected amino,

hydroxyl or carboxyl group may be achieved using standard alkylation or esterification procedures, for example as described below.

Thus according to a further aspect of the invention a compound of formula (1) may be prepared by coupling an acid of formula (2)



or an active derivative thereof, with an amine of formula (3)



followed by removal of any protecting groups.

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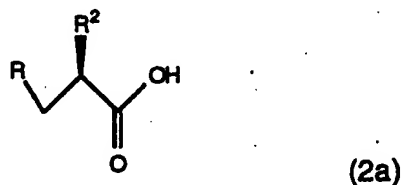
Active derivatives of acids of formula (2) include for example acid anhydrides, or acid halides, such as acid chlorides.

The coupling reaction may be performed using standard conditions for amination reactions of this type. Thus, for example the reaction may be achieved in a solvent, for example an inert organic solvent such as an ether, e.g. a cyclic ether such as tetrahydrofuran, an amide e.g. a substituted amide such as dimethylformamide, or a halogenated hydrocarbon such as dichloromethane at a low temperature, e.g. -30°C to ambient temperature, such as -20°C to 0°C, optionally in the presence of a base, e.g. an organic base such as an amine, e.g. triethylamine or a cyclic amine such as N-methylmorpholine. Where an acid of formula (2) is used, the reaction may additionally be performed in the presence of a condensing agent, for example a diimide such as N,N'-dicyclohexylcarbodiimide, or 1-(3-dimethylaminopropyl)-3-ethylcarbodi-imide, advantageously in the presence of a triazole such as 2-hydroxy-benzotriazole. Alternatively, the acid may be reacted with a chloroformate for example ethylchloroformate, prior to reaction with the amine of formula (3).

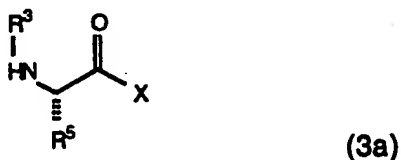
30

Free hydroxyl or carboxyl groups in the starting materials of formula (2) [where R is -CONHOH or CO₂H] and (3) may need to be protected during the coupling reaction. Suitable protecting groups and methods for their removal may be those mentioned above. Where R in the intermediates of formula (2) is a -P(O)(X¹R⁷)X²R⁸ group, at least one of R⁷ or R⁸ is other than a hydrogen atom. Conveniently, each of R⁷ and R⁸ is an optionally substituted alkyl, aryl or aralkyl group. Such groups, when present in compounds of the invention may be cleaved as described below to yield other compounds of the invention wherein R⁷ and/or R⁸ is each a hydrogen atom.

It will be appreciated that where a particular stereoisomer of formula (1) is required, this may be obtained by resolution of a mixture of isomers following the coupling reaction of an acid of formula (2) and an amine of formula (3). Conventional resolution techniques may be used, for example separation of isomers by chromatography e.g. by use of high performance liquid chromatography. Where desired, however, appropriate homochiral starting materials may be used in the coupling reaction to yield a particular stereoisomer of formula (1). Thus, in particular process a compound of formula (1a) may be prepared by reaction of a compound of formula (2a)



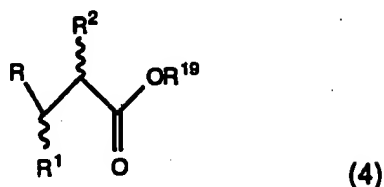
with an amine of formula (3a)



as described above

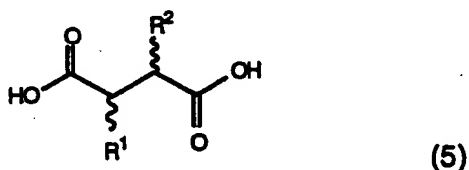
Intermediate acids of formula (2) wherein R is a carboxyl or esterified carboxyl group or a group -P(O)(X¹R⁷)X²R⁸ or -SR⁶ may be prepared

from a corresponding ester of formula (4)



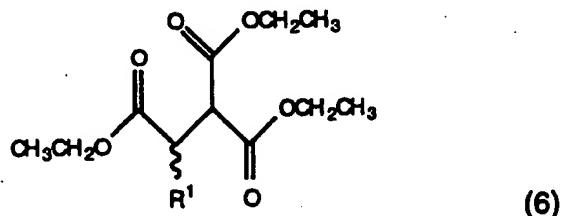
- where R¹⁹ is an alkyl group, for example a methyl or t-butyl group, using for example trifluoroacetic acid, or, when R¹⁹ is an aralkyl group, such as a benzyl group, by hydrogenolysis, for example by reaction with hydrogen in the presence of a metal catalyst, e.g. palladium, on a support such as carbon in a solvent such as an alcohol, e.g. methanol optionally at an elevated pressure and temperature.

- 10 An ester of formula (4) where R is a carboxyl or esterified carboxyl group may be prepared by esterification of the corresponding acid of formula (5)



- 15 using an appropriate acyl halide, for example an acyl chloride in a solvent such as an alcohol, e.g. methanol at a low temperature, e.g. around 0°C.

Acids of formula (5) may be prepared by alkylation of a compound of formula (6)



- 20 with an appropriate halide, e.g. a compound R²Hal, where Hal is a halogen atom such as a chlorine or bromine atom in the presence of a base, for example an alkoxide such as sodium ethoxide in a solvent such as an alcohol, e.g. ethanol at ambient temperature, followed by
- 25 decarboxylation using for example concentrated hydrochloric acid at an

levated temperature, e.g. the reflux temperature.

Intermediates of formula (6) are either known compounds or may be prepared by methods analogous to those used for the preparation of the known compounds.

Intermediate esters of formula (4) where R is a $-P(O)(X^1R^7)X^2R^8$ group may be prepared by reaction of an acrylate $R^1CHC(R^2)COR^{19}$ with a phosphite: $P(OR^{20})(X^1R^7)X^2R^8$ [where R^{20} is a leaving group, for example a silyl group such as a trialkylsilyl group e.g. a trimethylsilyl group] at an elevated temperature.

Acrylates of formula $R^1CHC(R^2)COR^{19}$ may be prepared by reaction of a mono-ester $HOOCCH(R^2)COOR^{19}$ with an aldehyde R^1CHO or a polymer thereof e.g. paraformaldehyde or paraldehyde in the presence of a base, for example an organic base such as piperidine. The reaction may be performed in a solvent, such as pyridine, optionally at an elevated temperature.

Mono-esters of formula $HOOCCH(R^2)COOR^{19}$ may be prepared by hydrolysis of the corresponding di-ester $R^{19}OOCCH(R^2)COOR^{19}$ using a base, for example an alkali hydroxide, in an inert solvent such as dioxane at a low temperature e.g. around $0^\circ C$. The di-esters for use in this reaction may be prepared by alkylation of the corresponding malonates of formula $R^{19}OOCCH_2COOR^{19}$ with a halide R^2Hal [where Hal is a halogen atom such as a chlorine or bromine atom] in the presence of a base, e.g. a hydride such as sodium hydride in a solvent such as tetrahydrofuran at ambient temperature. Malonates of formula $R^{19}OOCCH_2COOR^{19}$ are either known compounds or may be prepared by methods analogous to those used for the preparation of the known compounds.

Intermediate phosphites of formula $P(OR^{20})(X^1R^7)X^2R^8$ may be prepared by reaction of a phosphite $HP(O)(X^1R^7)X^2R^8$ with an appropriate amine $(R^{20})_2NH$ e.g. a silazane, at an elevated temperature, e.g. the reflux temperature. Phosphites of formula $HP(O)(X^1R^7)X^2R^8$ are either known

compounds or may be prepared by methods analogous to those used for the preparation of the known compounds.

- Intermediates of formula (4) where R is a $-SR^6$ group are either known compounds or may be prepared from known starting materials of formula $R^6SCH(R^1)CH(CO_2CH_2CH_3)_2$ by using a similar series of reactions to those just described for the preparation of compounds of formula (4) where R is a carboxyl group.
- 10 In another process, intermediate acids of formula (2) wherein R is a $-P(O)(X^1R^7)X^2R^8$ group may be prepared by reaction of an acid $R^2CH_2CO_2H$ with a phosphonate $P(O)(X^1R^7)(X^2R^8)CH_2OR^{21}$ where R^{21} is a leaving group, for example a trifluoromethylsulphonyloxy group in the presence of a base such as n-butyllithium in a solvent such as tetrahydrofuran. Phosphonates for use in this reaction may be prepared from the corresponding compound $P(O)(X^1R^7)(X^2R^8)CH_2OH$ by reaction with paraformaldehyde in the presence of a base such as triethylamine at an elevated temperature followed by reaction with a halide $R^{21}Hal$ in the presence of a base such as sodium hydride in a solvent such as an ether. Phosphonates $P(O)(X^1R^7)(X^2R^8)CH_2OH$ and acids $R^2CH_2CO_2H$ for use in the above reactions are either known compounds or may be prepared by methods analogous to those used for the preparation of the known compounds.
- 25 Intermediate acids of formula (2) wherein R is a $-CONHOR^6$ group or a protected derivative thereof may be prepared by reaction of an anhydride of formula (7)



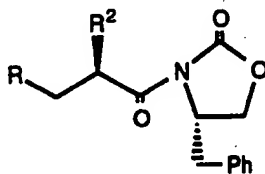
(7)

- with a hydroxylamine such as O-benzylhydroxylamine or NH_2OR^6 where R^6 is an acyl group in a solvent such as tetrahydrofuran at a low temperature, e.g. around $-20^\circ C$, followed where desired by removal of

the protecting group as described above.

The intermediate anhydrides of formula (7) may be prepared for example by heating for example at the reflux temperature, a diacid of formula (5) where R is $-\text{CO}_2\text{H}$ with an acyl chloride such as acetyl chloride.

The homochiral acids of formula (2a) may be prepared according to another feature of the invention by oxidation of an oxazolidinone of formula (8)



(8)

(where Ph is a phenyl group)

using an oxidising agent such as peroxide, e.g. hydrogen peroxide in a solvent such as an ether e.g. a cyclic ether such as tetrahydrofuran, at a low temperature, e.g. around 0°C followed by treatment with a base, such as lithium hydroxide, at an elevated temperature.

The compounds of formula (8) may be prepared by reaction of an acyl halide $\text{RCH}_2\text{CH}(\text{R}^2)\text{COHal}$ (where Hal is a halogen atom such as a chlorine, bromine or iodine atom) with a solution of (S)-4-(phenylmethyl)-2-oxazolidinone in the presence of a base such as n-butyl lithium in a solvent such as tetrahydrofuran at a low temperature, e.g. around -78°C .

Acyl halides $\text{RCH}_2\text{CH}(\text{R}^2)\text{COHal}$ may be prepared by treatment of the corresponding known acids $\text{RCH}_2\text{CH}(\text{R}^2)\text{CO}_2\text{H}$ with conventional halogenating agents for example thionyl halides under standard reaction conditions.

Intermediates of formula (3) are either known compounds or may be prepared from known amino acid starting materials using standard methods, for example by employing a series of substitution reactions to manipulate the groups R^5 and X as described in the Examples

hereinafter or for example as described by L. Wessjohann *et al.* Chem. Ber. 1992, 125, 867-882.

- 5 Compounds of formula (1) may also be prepared by interconversion of other compounds of formula (1). Thus, for example, a compound of formula (1) wherein R is a $-\text{CONHOR}^6$ group may be prepared by reaction of a corresponding acid of formula (1) wherein R is a $-\text{CO}_2\text{H}$ group or an active derivate thereof (for example an acid chloride or an acid anhydride) with hydroxylamine or an O-protected derivative or a salt thereof or a reagent R^6ONH_2 where R^6 is an acyl group. The reaction may be performed using the reagents and conditions described above in the preparation of compounds of formula (1) from the starting materials of formulae (2) and (3).
- 10
- 15 In another interconversion process, compounds of formula (1) wherein R is $-\text{CO}_2\text{H}$ and/or X contains a $-\text{CO}_2\text{H}$ group may be prepared by hydrolysis of the corresponding esterified compounds (for example where R is a $-\text{CO}_2\text{R}^{13}$ group and/or X contains a similar group) using conventional procedures, for example by treatment with a base, e.g. an alkali metal hydroxide such as lithium hydroxide in a solvent such as an aqueous alcohol, e.g. aqueous methanol, or by treatment with an acid such as a mineral acid, e.g. hydrochloric acid in the presence of a solvent, e.g. dioxane.
- 20
- 25 Similarly esters of formula (1), for example where R is a CO_2R^{13} group and/or X contains a $-\text{CO}_2\text{R}^{13}$ group may be prepared by reaction of the corresponding acids, where R is a $-\text{CO}_2\text{H}$ group and/or X contains a $-\text{CO}_2\text{H}$ group or an active derivative thereof, with an alcohol R^{13}OH using standard conditions.
- 30
- 35 In another interconversion process, a compound of formula (1) wherein R^5 is a group $-\text{C}(\text{R}^9)(\text{R}^{10})\text{SR}^{11}$ may be oxidised to a corresponding compound where R^5 is a group $-\text{C}(\text{R}^9)(\text{R}^{10})\text{SOR}^{11}$ or $-\text{C}(\text{R}^9)(\text{R}^{10})\text{SO}_2\text{R}^{11}$ using an oxidising agent, for example a peroxy-monosulphate such as potassium peroxymonosulphate, in a solvent such as an aqueous alcohol at ambient temperature or a peroxy-acid in a

halogenated hydrocarbon solvent such as dichloromethane at a low temperature, e.g. around -78°C.

5 The compounds according to the invention are potent and selective inhibitors of gelatinase and advantageously have a long duration of action when administered orally. The activity and selectivity of the compounds may be determined by the use of appropriate enzyme inhibition tests for example as described in Example A hereinafter or by
10 administration to mice as described hereinafter in Example B. In our tests using this approach, compounds according to the invention have been shown to inhibit gelatinase with K_i values in the picomolar-nanomolar range and to have around a 100 fold or greater selectivity for gelatinase over stromelysin, and around a 1000-fold or greater selectivity for gelatinase over collagenase.

15 The compounds according to the invention can be expected to be of use in the prophylaxis or treatment of diseases or disorders in which stromelysin, collagenase and, in particular, gelatinase have a role. Thus for example the compounds of formula (1) may be of use in the
20 prophylaxis or treatment of musculo-skeletal disorders, for example arthritic diseases such as rheumatoid arthritis, osteoarthritis and septic arthritis, and to be of use to prevent tumour cell metastasis and invasion. The compounds may therefore be of use in the treatment of cancer, particularly in conjunction with radiotherapy, chemotherapy or surgery, or
25 in patients presenting with primary tumours, to control the development of tumour metastasis. Particular cancers may include breast, melanoma, lung, head, neck or bladder cancers. Other uses to which the compounds of the invention may be put, include use for prevention of myelin degradation in the central and peripheral nervous system, for
30 example in the treatment of multiple sclerosis, use for controlling periodontal diseases such as gingivitis, and use in tissue remodelling.

The compounds according to the invention can also be expected to be of use in the prophylaxis or treatment of angiogenic diseases. Such
35 diseases may be characterised by the pathological growth of new capillaries [see, for example Folkman, J. and Klagsbrun, M. Science 235,

442-447 (1987) and Moses, M. A. and Langer, R. Bio/Technology 9, 630-634 (1991)]. Particular angiogenesis dependent diseases include solid tumours and arthritic diseases as described above, and, additionally, psoriasis, eye diseases such as the proliferative retinopathies, neovascular glaucoma and ocular tumours, angiofibromas, and hemangiomas.

For use according to this aspect of the invention, the compounds of formula (1) may be formulated in a conventional manner, optionally with one or more physiologically acceptable carriers, diluents or excipients.

Thus according to a further aspect of the invention we provide a pharmaceutical composition comprising a compound of formula (1) and a pharmaceutically acceptable diluent, carrier or excipient.

In a still further aspect the invention provides a process for the production of a pharmaceutical composition comprising bringing a compound of formula (1) into association with a pharmaceutically acceptable diluent, carrier or excipient.

Compounds for use according to the present invention may be formulated for oral, buccal, parental or rectal administration or in a form suitable for nasal administration or administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution

with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles; and preservatives. The preparations may also
5 contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

10

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

15

The compounds of formula (1) may be formulated for parental administration by injection e.g. by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents.

20

Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

25

The compounds of formula (1) may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

30

In addition to the formulations described above the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

35

For nasal administration or administration by inhalation the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon

dioxide or other suitable gas, or mixture of gases.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispenser device may be accompanied by instructions for administration.

The doses of compounds of formula (1) used in the above applications will vary depending on the disease or disorder and condition of the patient to be treated but in general may be in the range around 0.05mg to 100mg/kg body weight, particularly from about 0.5mg to 50mg/kg body weight. Dosage units may be varied according to the route of administration of the compound in accordance with conventional practice.

DESCRIPTION OF SPECIFIC EMBODIMENTS

The invention is further illustrated in the following non-limiting Examples.

In the Examples, the following abbreviations are used:

RT	-	room temperature
DMF	-	dimethylformamide
THF	-	tetrahydrofuran
TFA	-	trifluoroacetic acid
CH ₂ Cl ₂	-	dichloromethane
Et ₂ O	-	diethylether

EXAMPLE A

The activity and selectivity of the compounds of the invention may be determined as described below.

All enzyme assays to determine K_i values were performed using the peptide substrate Dnp-Pro-Leu-Gly-Leu-Trp-Ala-D-Arg-NH₂. [M. Sharon Stock and Robert D. Gray. JBC 264, 4277-81, 1989]. The enzymes cleave at the Gly-Leu bond which can be followed fluorimetrically by

measuring the increase in Trp fluorescence emission associated with the removal of the quenching dinitrophenol (Dnp) group.

Essentially, enzyme (e.g. gelatinase, stromelysin, collagenase) at 0.08-2nM; a range of inhibitor concentrations (0.1-50 x K_i) and substrate (approx. 20 μ M) are incubated overnight in 0.1M Tris/HCl buffer, pH 7.5, containing 0.1M NaCl, 10mM CaCl_2 and 0.05% Brij 35 at either room temperature or 37°C depending on the enzyme. The reaction is stopped by adjusting the pH to 4 using 0.1M sodium acetate buffer and the fluorescence read at an excitation wavelength of 280nm and emission wavelength of 346nm.

K_i values can be established using the equation for tight-binding inhibition:-

$$V_i = \frac{V_o}{2[E]} \left(\sqrt{(K_{i(\text{app})} + [I])^2 + 2(K_{i(\text{app})} - [I])[E] + [E]^2} - (K_{i(\text{app})} + [I] - [E]) \right)$$

where V_o is the initial rate of reaction in the absence of inhibitor, V_i is the initial rate in the presence of inhibitor, $[E]$ is the total enzyme concentration and $[I]$ the total inhibitor concentration in the reaction mixture.

For stromelysin and collagenase, K_i (app) was assumed to approximate to the true K_i as $[S] \ll K_m$ for the substrate hydrolysis. For gelatinase the K_i was determined by performing the analyses at several substrate concentrations. A plot of K_i (app) vs. $[S]$ then gave the true K_i as the value of the y-axis intercept.

The following results were obtained with compounds according to the invention:

<u>Compound of</u> <u>Example No.</u>	<u>K_i (nM)</u>		
	Collagenase	Stromelysin-1	Gelatinase -72KD
3a)	26.3	5.3	0.005
3b)	122	3.6	0.027

4

20.7

5.92

0.005

EXAMPLE B

5 The oral activity of the compounds according to the invention may be determined using the mouse pleural cavity assay described below. This assay measures the ability of compounds of the invention when administered orally to inhibit a subsequent inoculation of gelatinase into the mouse pleural cavity.

10 A 2ml solution of the test compound (for example around 25µm/Kg) in an appropriate solvent (e.g. 50% polyethylene glycol (PG)) plus a variable proportion of dimethyl sulphoxide (DMSO) (if required) is administered orally. After an interval of up to 24 hrs, 0.4ml of a mixture of an equal
15 volume (2.2ml) of the enzyme gelatinase A (72K form at a concentration of 20nM) and radiolabelled [¹⁴C]-gelatin (at an approximate concentration of 10µM i.e. 500 times molar excess) is injected into the pleural cavity and maintained at 4°C. After 35 min mice are overdosed with anaesthetic, the contents of the pleural cavity aspirated and the aspirates cleared by centrifugation at 4°C then diluted to 15% in
20 trichloroacetic acid (TCA) and left overnight at 4°C. The resulting TCA precipitate is then separated by centrifugation and radioactivity in each supernatant measured by scintillation counting. Results are expressed as a % inhibition of enzyme activity calculated by comparing the radioactivity measured for each test compound with a control value
25 obtained by performing the same assay in the absence of a gelatinase inhibitor. Thus, for example, the compound of Example 3b) gave 100% inhibition when administered orally at the above dose.

30 The ability of compounds of the invention to prevent tumour cell invasion may be demonstrated in a standard mouse model. Thus, briefly, nude mice may be inoculated with a tumour cell line showing gelatinase - dependent invasion and the ability of compounds according to the invention to reduce subsequent lung tumour colonisation may be evaluated in accordance with standard procedures. In out tests,
35 compounds according to the invention, when administered orally in a single dose at 100mg/kg to mice in the above model have reduced lung

tumour colonisation to negligible levels for periods of twelve hours duration or longer.

In general, compounds according to the invention are non-toxic at pharmaceutically useful doses. Thus, for example, when the compounds were administered to mice at the doses described above no adverse effects were observed.

INTERMEDIATE 1

N-tert-butoxycarbonyl-L-penicillamine

To a solution of L(+)- penicillamine (24g; 161mmol) in 10% w/v aqueous sodium carbonate solution (300ml) was added di-tert-butyl dicarbonate (35.1g; 161mmol) in tert-butanol (300ml). After stirring the reaction mixture for 18 hr at RT, the volume was reduced by approximately one half under reduced pressure and the pH was adjusted to 2 using 1N hydrochloric acid. The resulting slurry was extracted several times with Et₂O, the ethereal layers being combined, dried (MgSO₄) and evaporated to give the title compound (36.7g) as a clear gum. δ_H (CDCl₃) 8.65 (1H, br s), 5.50 (1H, d), 4.35 (1H, d), 2.00 (1H, br s), 1.60 (3H, s), 1.50 (9H, s), and 1.45 (3H, s).

INTERMEDIATE 2

N-tert-butoxycarbonyl-L-penicillamine-N-methylamide

A solution in anhydrous dimethylformamide (250ml) of Intermediate 1 (11.69g; 33.5mmol), N-hydroxybenzotriazole (4.53g; 33.5mmol), methylamine hydrochloride (11.3g; 167.5 mmol), N-methylmorpholine (20.6ml; 184mmol), 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (7.1g; 36.9mmol) and a trace of 4-dimethylaminopyridine was stirred at RT under an atmosphere of nitrogen for 18 hr. The reaction mixture was poured into 10% w/v aq.citric acid (600ml) and extracted into Et₂O (600ml). The organic layer was separated, washed with 10% w/v aq. NaHCO₃ solution (500ml), dried (MgSO₄) and evaporated. Following chromatography (SiO₂; EtOAc 20-50% in hexane), the title compound (6.36g) was obtained as a clear glass. δ_H (CDCl₃) 6.85 (1H, m), 5.75 (1H, d), 4.15 (1H, d), 2.75 (3H, d), 2.50 (1H, br s), 1.50 (3H, s), 1.45 (9H, s), and 1.35 (3H, s).

INTERMEDIATE 3**N-tert-butoxycarbonyl-L-[S-(methyl)penicillamine]-N-methylamide**

- 5 To a solution of Intermediate 2 (1g; 3.82mmol) in 2N aq. NaOH/CH₃OH (10ml/30ml) was added iodomethane (1.18ml; 19mmol) in CH₃OH (4ml). After stirring at RT for 2 hr, the reaction mixture was concentrated to one quarter volume, then partitioned between Et₂O and brine. The organic layer was washed with 10% w/v aq. citric acid, dried (MgSO₄) and
- 10 evaporated to give the title compound (810mg) as a colourless glass. δ_H (CDCl₃) 6.80 (1H, m), 5.65 (1H, d), 4.20 (1H, d), 2.80 (3H, s), 2.10 (3H, s), 1.45 (9H, s), 1.40 (3H, s), and 1.30 (3H, s).

INTERMEDIATE 4

- 15 a) **L-[S-(Methyl)penicillamine]-N-methylamide trifluoroacetate**

A solution of Intermediate 3 (810mg; 2.93mmol) in TFA/CH₂Cl₂ (10ml/10ml) was stirred at RT for 2 hr. The solvent was then removed under reduced pressure with the aid of a toluene/THF azeotrope. The

20 title compound (855mg) was obtained as a yellow tinged glass in quantitative yield. δ_H (CDCl₃) 8.4 (3H, br s), 7.9 (1H, q), 4.20 (1H, s), 2.80 (3H, d), 2.0 (3H, s), 1.45 (3H, s), and 1.35 (3H, s).

- 25 b) **3-(3-Aminopropylthio)-2(S)-benzyloxycarbonylamino-3-methylbutanoic acid trifluoroacetate**

From Intermediate 14 (6.4g; 14.5mmol) in TFA/CH₂Cl₂ (6ml/6ml), using the method described to obtain Intermediate 4a), to give the title compound (6.04g).

- 30 **INTERMEDIATE 5**

3-[4-Phenoxybutanoyl]-4(S)-benzyl-2-oxazolidinone

- 4-Phenoxybutyric acid (1.22g, 6.8mmol, 1.2 equiv) was heated to reflux with thionyl chloride (0.66ml, 1.07g, 9.0mmol, 1.6 equiv) for 30 min. The excess thionyl chloride was then removed under vacuum, the residue
- 35 dissolved in THF (10ml), and added to a cold (-78°C) solution of lithiated (S)-4-benzyl-2-oxazolidinone [prepared from the oxazolodinone (1g,

5.6mmol) and n-butyllithium (1.6M solution, 4.23ml, 6.8mmol, 1.2 equiv) in THF (25ml)]. The reaction mixture was stored for 2 hr at -78°C, then quenched with a 1:1 mixture of saturated brine and 10% HCl acid (20ml). The mixture was allowed to warm to RT and partitioned between ethyl acetate and water. The layers were separated and the aqueous layer washed twice with ethyl acetate. The combined organic layers were washed once with brine, once with sodium bicarbonate solution, dried (MgSO₄) and the solvent removed under vacuum to give a brown oil which was recrystallised (ethyl acetate) to give the title compound (0.897g) as a white solid. δ_H (CDCl₃) 7.35-7.17 (m, 7H), 6.94-6.86 (m, 3H), 4.66 (m, 1H), 4.18 (m, 2H), 4.06 (t, 2H), 3.30 (dd, 1H), 3.16 (t, 2H), 2.25 (dd, 1H), and 2.18 (m, 2H).

INTERMEDIATE 6

3-(1-Oxo-2(R)-t-butyl-acetyl-2-phenoxyethyl)-4(S)-benzyl-2-oxazolidinone

Sodium hexamethyldisilazide (1.0M solution in THF, 4.2ml, 4.2mmol, 1.4 equiv) was added dropwise to a solution of Intermediate 5 (1.01g, 3mmol) in THF (25ml) at -78°C. Stirring was continued at this temperature for 1 hr, then (t)-butyl bromoacetate (1.74g, 1.44ml, 9mmol, 3 equiv) was added. The temperature was allowed to rise to -20°C over a period of 4 hr. The reaction was then cooled to -78°C and quenched with a mixture of brine and 10% HCl acid (1:1, 20ml). The reaction was warmed to RT and partitioned between water and ethyl acetate. The aqueous layer was washed twice with ethyl acetate and the combined organic layers washed once with sodium bicarbonate solution, once with brine, dried (MgSO₄) and the solvent removed in vacuo to give a yellow oil. Chromatography (SiO₂ Merck 9385; ethyl acetate-hexane, 1:4) afforded the title compound (0.90g) as a white solid. δ_H (CDCl₃) 7.40-7.18 (m, 7H), 6.95-6.80 (m, 3H), 4.62 (m, 1H), 4.42 (m, 1H), 4.28-3.96 (m, 3H), 3.87 (t, 1H), 3.33 (dd, 1H), 2.91 (dd, 1H), 2.72 (dd, 1H), 2.56 (dd, 1H), 2.26-1.94 (m, 2H), and 1.42 (s, 9H).

INTERMEDIATE 7

a) 2-(R)-(2-Phenoxyethyl)succinic acid-4-(t)-butyl monoester

Hydrogen peroxide (0.91ml, 8mmol, 4 equiv 27.5 wt%) was added to a cold (0°C) solution of Intermediate 6 (0.90g, 2mmol) in THF/water (4:1, 50ml). The solution was stirred for 5 min then a solution of lithium hydroxide (80mg, 2mmol) in water (10ml) was added dropwise. The reaction was stirred for 2 hr at 0°C then most of the THF was removed in vacuo. The mixture was partitioned between water and CH₂Cl₂, and the aqueous layer was extracted with ethyl acetate (x3). The combined organic layers were dried (MgSO₄) and the solvent removed to give the title compound (0.60g) as a colourless oil which was used without further purification.

b) 2-(R)-[3-(4-methoxyphenyl)propyl]succinic acid-4-(t)-butyl monoester

The above intermediate was prepared in a similar manner to Intermediate 7a) starting from 4-(4-methoxyphenyl)butyric acid.

c) 2-(R)-[3-(4-methylphenyl)propyl]succinic acid-4-(t)-butyl monoester

The above intermediate was prepared in a similar manner to Intermediate 7a) starting from 4-(4-methylphenyl)butyric acid.

INTERMEDIATE 8

2-(R)-[3-(4-Chlorophenyl)propyl]succinic acid-4-(t)-butyl monoester

The title compound was prepared in a similar manner to Intermediate 7a) starting from 4-(4-chlorophenyl)butyric acid (see also J R Porter *et al*, "Organometallic Reagents in Organic Synthesis", SmithKline Beecham Research Symposium, 25th-26th March, 1993, Robinson College, Cambridge, UK).

INTERMEDIATE 9

Methyl 2-chloro-2-cyclopropylidino acetate

To a solution of sodium methoxide in methanol [prepared from sodium (8.22g) in methanol (250ml)] was added 1-chloro-1-(trichloroethenyl)-cyclopropane (15ml) and the mixture heated under reflux for 87hr. The

- reaction mixture was cooled, treated with ice-water (100ml), brine (100ml), extracted with Et₂O (4 x 250ml), the combined organic layers dried (MgSO₄) and concentrated *in vacuo*. The residue was dissolved in CH₂Cl₂ (250ml) before adding the ion exchange resin (Dowex 50W-X8) (10.0g) and some 3Å molecular sieves. The mixture was stirred at RT for 48h, filtered through celite and concentrated *in vacuo*. The residue was chromatographed (SiO₂; EtOAc-Pentane, 1:8), to give the title compound (5.64g) as a white solid.

10 INTERMEDIATE 10

Methyl 2-azido-2-(1-methylthiocyclopropyl)acetate

- To a suspension of sodium thiomethoxide (1.43g) in THF (35ml) at -78°C was added Intermediate 9 (2.58g) in THF (25ml), the mixture stirred at -78°C for 4hr, then warmed up to -20°C and stored at -18°C. The mixture was treated with 2.0M hydrochloric acid in Et₂O (1eq), stirred at -20°C for 5hr, treated with saturated ammonium chloride and extracted with Et₂O. The combined organic layer was dried (MgSO₄) and concentrated *in vacuo* to give methyl 2-chloro-2-(1-methylthiocyclopropyl) acetate (2.23g) as a colourless oil.
- A mixture of this compound (2.23g) aliquat® 336 (5.23ml), and sodium azide (2.22g) in water (15ml) was stirred vigorously at 55°C for 48hr. The reaction mixture was extracted with Et₂O, the combined organic layer washed with brine, dried (MgSO₄) and concentrated *in vacuo*. Chromatography (SiO₂; Et₂O-pentane, 1:6) gave the title compound (0.7492g) as a colourless oil.

INTERMEDIATE 11

2-Azido-2-(1-methylthiocyclopropyl)ethanamide

- A solution of Intermediate 10 (0.72g) in methanol (20ml) was heated with aqueous sodium hydroxide (2.0M; 2.7ml) and water (2.7ml) and the mixture stirred at RT overnight. The solvent was removed *in vacuo*, the residue dissolved in water, extracted with Et₂O then acidified to pH3 with aqueous hydrochloric acid (2.0M). The solution was extracted with chloroform, the combined organic layer dried (MgSO₄) and concentrated *in vacuo* to give 2-azido-2-(1-thiomethyl)cyclopropylidino acetic acid (0.56g) as a thick pale lemon oil.

A solution of the acid (0.56g) in THF (25ml) was treated with N-methylmorpholine (413 μ l) and isobutylchloroformate (430 μ l) at -30°C and the mixture stirred at -30 to -25°C for 1hr. Concentrated aqueous ammonia (~35%; 1.6ml) was added and the stirred reaction mixture
5 allowed to warm up to RT overnight. The solvent was removed *in vacuo* and the residue partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. The aqueous layer was extracted with ethyl acetate and CH₂Cl₂, then acidified to pH3 with aqueous HCl (2.0M), extracted with CH₂Cl₂ and the organic layer dried (MgSO₄).
10 Chromatography (SiO₂; 5% methanol in CH₂Cl₂) afforded the title compound (0.50g) as a pale brown oil.

INTERMEDIATE 12

2-Amino-2-(1-methylthiocyclopropyl)ethanamide

trifluoroacetate

A solution of Intermediate 11 (0.48g) and trifluoroacetic acid (25ml) in degassed methanol (47.5ml) was treated with 10% palladium on carbon (90.0mg) and the mixture stirred at RT under an atmosphere of hydrogen for 18hr. The solvent was removed *in vacuo* to give the title compound
20 (528mg) as a very pale buff solid.

INTERMEDIATE 13

N-tert-Butoxycarbonyl-L-(S-methyl)penicillamide

A mixture of Intermediate 1 (14.7g; 59mmol), ethyl chloroformate (8.2ml; 67.7mmol), and N-methylmorpholine (10.8ml; 96.8mmol) in dry THF
25 (250ml) was activated for 1hr at -20°C. The reaction mixture was cooled to -30°C, a solution of 2N ammonia in methanol (100ml; 200mmol) was added slowly by syringe and the mixture allowed to warm to RT overnight. The volatiles were removed, the residue was partitioned
30 between ethyl acetate and aqueous citric acid, the organic layer washed with aqueous NaHCO₃, separated, dried (MgSO₄) then evaporated to yield N-tert-butoxycarbonyl-L-penicillamide (11.04g).

To a portion of this thiol (5.02g; 22.25mmol) in 2N NaOH (60ml) and ethanol (180ml) was added methyl iodide (6.91ml; 111mmol) and the
35 mixture stirred at RT for 18hr. The solution was concentrated *in vacuo*, partitioned between Et₂O and brine, dried (MgSO₄) and concentrated *in*

vacuo. Column chromatography (SiO₂; 4% CH₃OH in CH₂Cl₂) yielded the title compound (3.03g) as an off-white solid.

INTERMEDIATE 14

5 2-(S)-Benzyloxycarbonylamine-3-[3-(t-butyloxycarbonyl-amino)propylthio]-3-methylbutanoic acid

To L-penicillamine (15.75g; 105.8mmol) was added a solution of KOH (12.4g; 222.2mmol) in water (250ml). When the solution was complete, Et₂O (100ml) was added and the solution cooled to 0°C. Benzyl chloroformate (14.9ml; 105.8mmol) was added dropwise and the stirred reaction mixture allowed to warm to RT. The layers were separated, the aqueous layer acidified to pH 1-1.5 with 1N hydrochloric acid, extracted with CH₂Cl₂ (x3) and dried (MgSO₄). The solvent was removed in vacuo to yield N-benzyloxycarbonyl-L-penicillamine (21.27g).

15 To a portion of this compound (7.8g; 27.6mmol) in 2N NaOH/ethanol (1:1) was added a solution of N-benzyloxycarbonyl-3-chloro-1-propylamine (6.4g; 33.1mmol) [prepared from 3-chloropropylamine hydrochloride (5g; 38mmol) in 10% NaOH/t-butanol (2/3; 100ml) and di-t-butyl-dicarbonate (9.2g; 42.3mmol) in t-butanol (50ml)] in ethanol and the mixture was stirred overnight at 40°C. The solvent was evaporated in vacuo, the residue partitioned between Et₂O and 10% aqueous citric acid, the organic layer washed with brine, dried (MgSO₄) and the solvent removed in vacuo to yield the title compound (6.4g).

25 INTERMEDIATE 15

3-(S)-Benzyloxycarbonylamino-2,2-dimethylperhydro-5-thiazoline-4-one

To a cold (0°C) solution of Intermediate 4b) (1.04g; 2.23mmol) in dry DMF (400ml) were added N-methylmorpholine (735μl; 669mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (642mg; 3.34mmol), 1-hydroxybenzotriazole hydrate (452mg; 3.34mmol) and a catalytic amount of 4-dimethylaminopyridine, the stirred reaction mixture allowed to warm to RT overnight then dried (MgSO₄). The solvent was removed in vacuo and the residue purified by column chromatography (SiO₂; 10-20% ethyl acetate/hexane) to yield the title compound (3.17g).

INTERMEDIATE 16**3-Amino-2,2-dimethylperhydro-5-thiazocine-4-one****5 hydrobromide**

A portion of Intermediate 15 (350mg) was treated with a solution of 30% HBr in acetic acid (10ml). The solvent was evaporated to dryness and the residue partitioned between water and Et₂O. The aqueous layer was separated then freeze-dried to yield the title compound (308mg) as a
10 pale yellow solid.

EXAMPLE 1**a) [4-t-Butoxy-2(R)-[3-(4-chlorophenyl)propyl]succinyl]-L-[S-(methyl)penicillamine]-N-methylamide**

15 A solution in anhydrous DMF (30ml) of Intermediate 8 (948mg; 2.9mmol), Intermediate 4a) (852mg; 2.93mmol) N-hydroxy-benzotriazole (397mg; 2.93mmol), N-methylmorpholine (983μl; 8.79mmol), 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (614mg; 3.19mmol) and a trace amount of 4-dimethylaminopyridine was stirred at RT under an atmosphere of
20 nitrogen for 18 hr. The reaction mixture was poured into 10% w/v aq.citric acid (100ml) and extracted into diethyl ether (100ml). The organic layer was washed with 10% w/v aq. NaHCO₃, separated, dried (MgSO₄) and evaporated. The residue was chromatographed (SiO₂; 2-4% CH₃OH in CH₂Cl₂) to give the title compound (904mg) as a white solid. δ_H (CDCl₃) 7.25 (2H, d),
25 7.10 (2H, d), 4.50 (1H, d), 2.80 (3H, d), 2.30-2.7 (5H, m), 2.10 (3H, s), 1.75-1.30 (4H, m), 1.45 (9H, s), 1.40 (3H, s), and 1.30 (3H, s).

30 The following compounds were prepared in a similar manner to the compounds of Example 1a).

b) [4-t-Butoxy-2(R)-(2-phenoxyethyl)succinyl]-L-[S-(methyl)penicillamine]-N-methylamide

35 From Intermediate 7a and Intermediate 4.

- c) 4-t-Butoxy-2(R)-[3-(4-chlorophenyl)propyl]succinyl-2-(S)-amino-3-hydroxy-3-methyl butanamide
From Intermediate 8 and 2-(S)-amino-3-hydroxy-3-methyl butanamide.
- 5 d) {4-t-Butoxy-2(R)-[3-(4-chlorophenyl)propyl]succinyl}-L-(1-methylthiocyclopropyl)glycinamide
From Intermediate 8 and Intermediate 12.
- 10 e) {4-t-Butoxy-2(R)-[3-(4-methoxyphenyl)propyl]succinyl}-L-(1-methylthiocyclopropyl)glycinamide
From Intermediate 7b and Intermediate 12.
- 15 f) t-Butoxy-N4-[3-(S)-(2,2-dimethyl-4-oxoperhydro-5-thiazocinyl)]-3-(R)-[3-(4-chlorophenyl)propyl]succinamate
From Intermediate 8 and Intermediate 16. The title compound was obtained as a colourless glass.

20 EXAMPLE 2

- a) [4-Hydroxy-2(R)-[3-(4-chlorophenyl)propyl]succinyl]-L-[S-(methyl)penicillamine]-N-methylamide
A solution of the compound of Example 1a) (452mg; 0.933mmol) in a mixture of TFA (10ml) and water (0.5ml) was left to stand at 4°C for 18 hr. The solvent was evaporated with the aid of a toluene/THF azeotrope. The title compound (400mg) was obtained as a colourless foam in quantitative yield. δ_H (CDCl₃) 10.20 (1H, br s), 7.65 (1H, d), 7.25 (2H, d), 7.05 (2H, d), 6.95 (1H, q), 4.65 (1H, d), 2.80 (3H, d), 2.80-2.40 (5H, m), 2.05 (3H, s), 1.40-1.70 (4H, m), 1.30 (3H, s), and 1.25 (3H, s).
- 25
- 30

The following compounds were prepared in a similar manner to the compound of Example 2a).

- 35 b) {4-Hydroxy-2(R)-[3-(4-chlorophenyl)propyl]succinyl}-2(S)-2-amino-3-hydroxy-3-methylbutanamide

From the compound of Example 1c).

- c) {4-Hydroxy-2(R)-[3-(4-chlorophenyl)propyl]succinyl}-L-(1-methylthiocyclopropyl)glycinamide

5 From the compound of Example 1d).

- d) {4-Hydroxy-2(R)-[3-(4-methoxyphenyl)propyl]succinyl}-L-(1-methylthiocyclopropyl)glycinamide

From the compound of Example 1e).

10

- e) Hydrogen-N4-[3-(S)-(2,2-dimethyl-4-oxoperhydro-5-thiazocinyl)]-3-(R)-[3-(4-chlorophenyl)propyl]succinamate

From the compound of Example 1f).

15

EXAMPLE 3

- a) [4-(N-Hydroxyamino)-2(R)-[3-(4-chlorophenyl)propyl]succinyl]-L-[S-(methyl)penicillamine]-N-methylamide

20 To a solution in anhydrous THF of the compound of Example 2a) (400mg; 0.933 mmol) at -20°C was added N-methylmorpholine (209µl; 1.87 mmol), and ethyl chloroformate (133µl; 1.12 mmol). After 1 hr, O-trimethylsilylhydroxylamine (3.75mmol) was added and the reaction mixture was allowed to warm to RT overnight. The solvent was evaporated under reduced pressure and the residue was partitioned between ethyl acetate and 10% w/v aq. citric acid. The organic layer was separated, dried (MgSO₄) and evaporated. The residue was purified (SiO₂; 5-10% CH₃OH in CH₂Cl₂) to give the title compound (165mg) as a white solid. δ_H (CD₃OD) 7.25 (2H, d), 7.15 (2H, d), 4.50 (1H, s), 2.90 (1H, m), 2.70 (3H, s), 2.50-2.70 (2H, m), 2.40 (1H, dd), 2.20 (1H, dd), 2.05 (3H, s), 1.40-1.70 (4H, m), 1.40 (3H, s), and 1.35 (3H, s).

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30

The following compounds were prepared by coupling (as described in Example 1) Intermediate 8, 7b) or 7c) and the appropriate amide to yield the corresponding t-butoxy derivatives which were hydrolysed (as described in Example 2) to give the

35

corresponding carboxylic acid derivatives. The acid derivatives were then treated as described in Example 3a) to yield the following N-hydroxyamino derivatives:

- 5 b) [4-(N-Hydroxyamino)-2(R)-[3-(4-chlorophenyl)propyl]-succinyl]-L-penicillamine amide
 δ_H (CD₃OD) 7.25 (2H, d), 7.15 (2H, d), 4.50 (1H, s), 2.90 (1H, m), 2.60 (2H, m), 2.40 (1H, dd), 2.20 (1H, dd), 1.40 (4H, m), 1.45 (3H, s), and 1.40 (3H, s).
- 10 c) [4-(N-Hydroxyamino)-2(R)-[3(4-chlorophenyl)propyl]-succinyl]-L-[S-(4-morpholinoethyl)penicillamine]-N-methylamide
 δ_H (CD₃OD) 7.25 (2H, d), 7.15 (2H, d), 4.50 (1H, s), 3.70 (4H, t), 2.90 (1H, m), 2.15-2.80 (13H, m), 1.40-1.70 (4H, m), 1.40 (3H, s), and 1.40 (3H, s).
- 15 d) [4-(N-Hydroxyamino)-2(R)-[3-(4-chlorophenyl)propyl]-succinyl]-L-penicillamine-N-methylamide
 δ_H (CD₃OD) 7.25 (2H, d), 7.15 (2H, d), 4.50 (1H, s), 2.90 (1H, m), 2.70 (3H, s), 2.60 (2H, m), 2.40 (1H, dd), 2.20 (1H, dd), 1.45-1.65 (4H, m), 1.40 (3H, s), and 1.35 (3H, s).
- 20 e) N-[4-(N-hydroxyamino)-2(R)-[3-(4-chlorophenyl)propyl]-succinyl]-2(S)-2-amino-3-hydroxy-3-methylbutanamide
 δ_H (CD₃OD) 1.23 (s, 3H, CH₃), 1.28 (s, 3H, CH₃), 1.40-1.64 (m, 4H, CH₂CH₂), 2.20 (dd, 1H, J 6.24, 14.6Hz, CH), 2.39 (dd, 1H, J 8.28, 14.6Hz, CH), 2.56-2.62 (m, 2H, CH₂), 2.82-2.98 (m, 1H, CH), 4.39 (s, 1H, CH), and 7.14-7.22 (AB, d, 4H, J 18.80Hz, Ar).
- 25 f) [4-(N-Hydroxyamino)-2-(R)-[3-(4-chlorophenyl)propyl]-succinyl]-L-(1-methylthiocyclopropyl)glycinamide
 δ_H (CD₃OD) 0.897 (m, 2H), 1.08 (m, 1H), 1.25 (m, 1H), 1.4-1.7 (m, 3H), 2.152 (s, 3H), 2.184 (dd, Q , 1H, J 7.7, 14.0Hz), 2.368 (dd, 1H, J =7.7Hz, 14.0Hz), 2.578 (m, 2H), 2.85 (m, 1H), 4.29 (s, 1H), 7.15 (d, 2H, J 8.5Hz), and 7.227 (d, 2H, J 8.5Hz).
- 30
- 35

- g) N-{4-(N-Hydroxyamino)-2(R)-[3-(4-methoxyphenyl)propyl]succinyl}-L-(1-methylthiocyclopropyl)glycinamide
 δ_H (CD₃OD) 0.89 (m, 2H, cyclopropyl CH), 1.03 (m, 1H, cyclopropyl CH), 1.22 (m, 1H), 1.4-1.7 (m, 4H), 2.184 (dd, Q, 1H, \downarrow 7.8, 14.5Hz), 2.367 (dd, 1H, \downarrow 7.8, 14.5Hz), 2.528 (m, 2H), 2.846 (m, 1H), 3.743 (s, 3H), 4.324 (s, 1H), 6.789 (d, 2H, \downarrow 6.0Hz), and 7.067 ppm (d, 2H, \downarrow 6.0Hz).
 Q overlapped with another signal.
- h) {4-(N-Hydroxyamino)-2(R)-[3-(4-methoxyphenyl)propyl]succinyl}-L-[S-(methyl)penicillamine]amide
 δ_H (CD₃OD) 6.90 (2H, d), 6.80 (2H, d), 4.55 (1H, m), 3.75 (3H, s), 2.85 (1H, m), 2.50 (2H, m), 2.40 (1H, dd), 2.20 (1H, dd), 2.10 (3H, s), 1.60 (4H, m), 1.40 (3H, s), and 1.35 (3H, s).
- i) {4-(N-Hydroxyamino)-2(R)-[3-(4-methylphenyl)propyl]succinyl}-L-[S-(methyl)penicillamine]amide
 δ_H (CD₃OD) 7.0 (4H, s), 4.50 (1H, d), 2.90 (1H, m), 2.55 (2H, m), 2.40 (1H, dd), 2.30 (3H, s), 2.20 (1H, dd), 2.05 (3H, s), 1.65 (4H, m), 1.40 (3H, s), and 1.35 (3H, s).
- j) N4-Hydroxy-N1-[3-(S)-(2,2-dimethyl-4-oxoperhydro-5-thiazocinyl)]-2-(R)-[3-(4-chlorophenyl)propyl]succinamide
 From the compound of Example 2e). δ_H (CD₃OD) 7.25 (2H, d), 7.15 (2H, d), 5.15 (1H, s), 3.85 (1H, m), 3.15 (1H, m), 2.95 (1H, m), 2.75 (2H, m), 2.60 (2H, m), 2.40 (1H, dd), 2.20 (1H, dd), 1.85 (2H, br m), 1.40-1.70 (4H, m) and 1.35 (6H, s).

EXAMPLE 4**{4-(N-Hydroxyamino)-2(R)-[3-(4-chlorophenyl)propyl]succinyl}-L-[S-(methyl)penicillaminesulphone]-N-methylamide**

To a solution of the compound of Example 3a) (452mg; 0.933mmol) in methanol (10ml) at 0°C was added a solution of Oxone® (1.844g; 3mmol) in water (5ml). The reaction mixture was allowed to warm to RT

over 3 days, then diluted with water and extracted into chloroform. The organic layer was washed with brine, dried (MgSO₄) and evaporated to give a quantitative recovery of the title compound (482mg) as a white solid. δ_H (CD₃OD) 7.25 (2H, d), 7.10 (2H, d), 5.0 (1H, s), 2.95 (3H, s), 2.90 (1H, m), 2.65 (3H, s), 2.60 (2H, m), 2.45 (1H, dd), 2.15 (1H, dd), 1.40-1.70 (10H, m).

EXAMPLE 5

{4-(N-Hydroxyamino)-2(R)-[3-(4chlorophenyl)propyl]succinyl)-L-[S-(methyl)penicillaminesulphoxide]-N-methylamide

To a solution of the compound of Example 3a (183.4mg; 0.379mmol) in CH₂Cl₂ (10ml) at -78°C, was added dropwise a solution of meta-chloroperbenzoic acid (78.3mg; 0.454mmol) in CH₂Cl₂ (1ml). The reaction mixture was then allowed to warm to RT and stirred for 2 hours. The solvent was removed under reduced pressure and the residue was purified (SiO₂; 4-5% CH₃OH in CH₂Cl₂), to give the title compound (117.3mg) as a 50:50 mixture of diastereoisomers. δ_H (CD₃OD) 7.25 (2H, m), 7.15 (2H, m), 4.70 (0.5H, s), 4.65 (0.5H, s), 2.90 (1H, m), 2.70 (3H, 2s), 2.10-2.65 (7H, m), 1.40-1.65 (4H, m), 1.40 (1.5H, s), 1.30 (3H, 2s) and 1.25 (1.5H, s).

EXAMPLE 6

{4-t-Butoxy-2-(R)-[3-(4-chlorophenyl)propyl]succinyl)-L-(S-methyl)penicillamide

A solution of Intermediate 13 (2.174g; 8.30mmol) in TFA/CH₂Cl₂ (20ml/20ml) was stirred at RT for 1hr. The solvent was then removed under reduced pressure with the aid of a toluene/THF/CH₂Cl₂ azeotrope to yield L-(S-methyl)penicillamide trifluoroacetate (quantitative) as a clear gum. A solution in anhydrous DMF of the penicillamide (8.3mmol), Intermediate 8 (7.9mmol), N-hydroxybenzotriazole (1.083g; 8mmol), N-methylmorpholine (2.24ml; 20mmol), 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (1.67g; 8.3mmol) and a trace of amount of 4-dimethylaminopyridine was stirred at RT under an atmosphere of nitrogen for 18hr. The reaction mixture was poured into 10% w/v aqueous citric acid and extracted into Et₂O. The organic layer was

separated, washed with 10% w/v aqueous NaHCO₃ solution, dried (MgSO₄) and evaporated to yield the title compound (2.9g) as a white foam.

5 **EXAMPLE 7**

[4-(N-Hydroxyamino)-2(R)-[3-(4-chlorophenyl)propyl]-succinyl]-L-[S-(methyl)penicillamine]amide

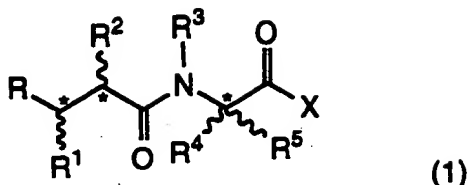
A solution of the compound of Example 6 (6.16mmol; 2.9g) in a mixture of TFA (40ml) and water (2ml) was left to stand at RT for 1hr. The solvent
10 was removed with the aid of a toluene/THF/CH₂Cl₂ azeotrope to yield {4-hydroxy-2-(R)-[3-(4-chlorophenyl)propyl]succinyl}-L-(S-methyl) penicillamide (quantitative) as a white solid.

To a solution in anhydrous THF of the acid (6.16mmol) at -20°C was added N-methylmorpholine (1.035ml; 9.24mmol), and ethyl
15 chloroformate (8.22μl; 6.78mmol). After 40min, O-trimethylsilylhydroxylamine (1.32ml; 12.32mmol) was added and the reaction mixture was allowed to warm to RT overnight. The solvent was evaporated under reduced pressure and the residue was partitioned between ethyl acetate and methanol and 10% w/v aqueous citric acid. The organic layer was
20 separated, dried (MgSO₄) and concentrated. A white solid appeared which was diluted with Et₂O and allowed to stand in the refrigerator overnight to yield, after filtration, the title compound (1.92g) as a white semi-crystalline material.

25 δ_H (CD₃OD) 7.25 (2H, d), 7.15 (2H, d), 4.50 (1H, s), 2.90 (1H, m), 2.60 (2H, m), 2.40 (1H, dd), 2.20 (1H, dd), 2.10 (3H, s), 1.60 (4H, m), 1.40 (3H, s), and 1.35 (3H, s).

CLAIMS

- 5 1. A compound of formula (1)



10 wherein R represents a -CONHOR⁶ [where R⁶ is a hydrogen atom or an acyl group], carboxyl (-CO₂H), esterified carboxyl, -SR⁶ or -P(O)(X¹R⁷) X²R⁸ group, where X¹ and X², which may be the same or different, is each an oxygen or sulphur atom and R⁷ and R⁸, which may be the same or different each represents a hydrogen atom or an optionally substituted alkyl, aryl, or aralkyl group;

15 R¹ represents a hydrogen atom or an optionally substituted alkyl, alkenyl, aryl, aralkyl, heteroaralkyl or heteroarylthioalkyl group;

20 R² represents a group -Z²(CH₂)_mZ¹-Ar wherein Ar is an aryl or heteroaryl group, Z¹ and Z², which may be the same or different, is each a bond or a heteroatom, and m is zero or an integer 1 to 6 with the proviso that when m is zero, Z² is a bond, and Z¹ is a heteroatom;

25 R³ represents a hydrogen atom or an alkyl group;

30 R⁴ represents a hydrogen atom or an alkyl group;

R⁵ represents a group -C(R⁹)(R¹⁰)Het-R¹¹, wherein R⁹ and R¹⁰ which may be the same or different is each an optionally substituted alkyl or alkenyl group optionally interrupted by one or more -O- or -S- atoms or -N(R¹²)- groups (where R¹² is a hydrogen atom or an optionally substituted alkyl group), or an optionally substituted cycloalkyl, cycloalkenyl, aryl or heteroaryl group, or R⁹ and R¹⁰ together with the carbon atom to which they are attached

are linked together to form an optionally substituted cycloalkyl or cycloalkenyl group; Het is -O-, -S(O)_p- [where p is zero, or an integer 1 or 2] or -N(R¹²)-, and R¹¹ is a hydrogen atom or an aliphatic, cycloaliphatic, heterocyclo-aliphatic, aromatic, or heteroaromatic group;

5

X is an amino (-NH₂), substituted amino, hydroxyl or substituted hydroxyl group, or is linked to the atom or group Het in R⁵ to form a chain -X-Alk-R⁵- where X is -N(R¹²)-, Alk is an optionally substituted alkylene chain and R⁵ is -Het-C(R⁹)(R¹⁰)-; and the salts, solvates, hydrates and prodrugs thereof.

10

2. A compound according to Claim 1 where R is a -CONHOH group.

15 3. A compound according to Claim 1 or 2 where R¹, R³ and R⁴ is each a hydrogen atom.

4. A compound according to any of Claims 1 to 3 where Ar is an optionally substituted phenyl group.

20

5. A compound according to any of Claims 1 to 4 where Z¹ and Z² is each a bond and m is an integer of value 3.

25

6. A compound according to any of Claims 1 to 5 where R⁹ and R¹⁰ is each a methyl group.

7. A compound according to any of Claims 1 to 6 where Het is a -S-atom.

30 8. A compound according to any of Claims 1 to 7 where R¹¹ is a hydrogen atom or a methyl group.

9. A compound according to any of Claims 1 to 8 where X is an amino (-NH₂) or a N-methylamino group.

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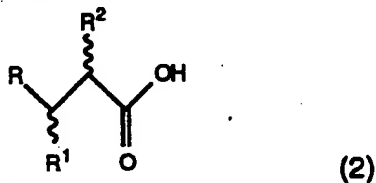
10. [4-(N-Hydroxyamino)-2(R)-[3-(4-chlorophenyl)propyl]succinyl]-L-

[S-(methyl)penicillamine] N-methylamide;
 [4-(N-Hydroxyamino)-2(R)-[3-(4-chlorophenyl)propyl]succinyl]-L-
 [S-(methyl)penicillamine] amide;
 [4-(N-Hydroxyamino)-2(R)-[3-(4-chlorophenyl)propyl]succinyl]-L-
 penicillamine amide;
 {4-(N-Hydroxyamino)-2(R)-[3-(4-chlorophenyl)propyl]succinyl}-L-
 [S-(methyl)penicillaminesulphone]-N-methylamide;
 {4-(N-Hydroxyamino)-2(R)-[3-(4-chlorophenyl)propyl]succinyl}-L-
 [S-(methyl)penicillaminesulphoxide]-N-methylamide; or
 {4-(N-Hydroxyamino)-2(R)-[3-(4-chlorophenyl)propyl]succinyl}-L-
 penicillamine-N-methylamide;
 and the salts, solvates, hydrates and prodrugs thereof.

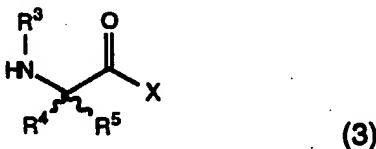
11. A pharmaceutical composition comprising a compound according
 to any of Claims 1 to 10 and a pharmaceutical diluent, carrier or
 excipient.

12. A process for preparing a compound of formula (1) as defined in
 Claim 1, which comprises:

a) coupling an acid of formula (2)



or an active derivative thereof, with an amine of formula (3)



followed by removal of any protecting groups; or

b) interconverting a compound of formula (1) to another
 compound of formula (1).

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 94/00895

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 5 C07C323/60 C07D295/08 C07C259/06 C07D285/38 C07C317/50
 A61K31/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 5 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,92 09564 (CELLTECH) 11 June 1992 cited in the application see page 2 - page 3 ----	1, 11, 12
A	EP,A,0 489 577 (CELLTECH) 10 June 1992 see page 2 - page 3 ----	1, 11, 12
A	WO,A,91 02716 (BRITISH BIO-TECHNOLOGY) 7 March 1991 see page 7 - page 9 -----	1, 11, 12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- * "A" document defining the general state of the art which is not considered to be of particular relevance
- * "E" earlier document but published on or after the international filing date
- * "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- * "O" document referring to an oral disclosure, use, exhibition or other means
- * "P" document published prior to the international filing date but later than the priority date claimed

* "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

* "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

* "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

* "&" document member of the same patent family

Date of the actual completion of the international search

17 June 1994

Date of mailing of the international search report

29. 06. 94

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Authorized officer

English, R

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB94/00895

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims 1,10: The term "prodrugs" is not clear and it is not possible to determine which compounds are meant by it. The scope of the search do not include prodrugs, except to the extent to which they may be covered by broad definition of the remaining part of the Markush formula in claim 1.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 94/00895

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9209564	11-06-92	AU-A- 9017391	25-06-92
		AU-A- 9023391	25-06-92
		EP-A- 0489577	10-06-92
		EP-A- 0489579	10-06-92
		WO-A- 9209565	11-06-92
		GB-A- 2255339	04-11-92
		GB-A- 2255340	04-11-92
		HU-A- 61973	29-03-93
		JP-T- 5503719	17-06-93
		JP-T- 5503720	17-06-93
		US-A- 5300501	05-04-94
EP-A-0489577	10-06-92	AU-A- 9017391	25-06-92
		AU-A- 9023391	25-06-92
		EP-A- 0489579	10-06-92
		WO-A- 9209564	11-06-92
		WO-A- 9209565	11-06-92
		GB-A- 2255339	04-11-92
		GB-A- 2255340	04-11-92
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		JP-T- 5503719	17-06-93
		JP-T- 5503720	17-06-93
		US-A- 5300501	05-04-94
WO-A-9102716	07-03-91	AU-B- 639706	05-08-93
		AU-A- 6045490	03-04-91
		EP-A- 0489032	10-06-92
		JP-T- 5501864	08-04-93